PRECURSORS TO RAPID ELEVATIONS IN INTRACRANIAL PRESSURE

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Abstract— **Intracranial pressure (ICP) monitoring and management have substantially improved the outcome of patients with traumatic brain injury (TBI). However, rapid elevations in ICP remain a significant problem as they may lead to secondary brain injury and worse outcome due to cerebral ischemia. Current therapy is targeted towards treating rapid ICP elevations after they occur. Ideally, anticipatory treatment to obviate any elevation in ICP could occur if reliable precursors to ICP elevation were determined. In this paper, we report evidence for a physiologic transition zone prior to rapid elevations in ICP. We found that in thirty-three episodes of ICP elevation recorded from eleven patients, there was a statistically consistent decrease in the cardiac component of the ICP signal and the coefficient of correlation between the ICP trend and the pulse amplitude. We conclude that specific ICP signal metrics may serve as precursors that characterize the transition zone prior to a rapid elevation and may enable prediction of these elevations up to thirty seconds ahead.**

Keywords— **Intracranial pressure, Intracranial hypertension, Cerebral Perfusion Pressure, Autoregulation, Time series Prediction, Traumatic brain injury, Head Injury**

I. Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children in the United States [1]. Elevated intracranial pressure (ICP) following TBI may result in secondary injury due to decreased cerebral perfusion pressure[1] (CPP) and cerebral ischemia[2]. ICP monitoring and therapeutic interventions to control elevated ICP ($>$ 20 mmHg) have resulted in improved outcomes [2–4]. However, current therapy is targeted towards treating rapid ICP elevations *after* they occur. Ideally, anticipatory treatment based on reliable detection of precursors could obviate elevations in ICP.

In many patients, including those with TBI, there is a natural progression of physiologic states from the time of injury, or onset of disease, through recovery or death [5]. The physiologic state of the patient may shift rapidly from from a compensated physiologic state to an uncompensated disease state. We hypothesize that there exist physiologic "transition zones" between compensated and uncompensated disease states, and that these transition zones may be detected by a careful analysis of physiologic signals. Accurate characterization of the transition zone prior to an uncompensated TBI state with an elevated ICP could lead to prophylactic therapy and could further improve outcome.

Other investigators have described a number of precursors to ICP elevations. Szewczykowski *et al.* described a "warning zone" in which the amplitude of ICP variations is strongly related to the mean ICP [6]. They hypothesized that this was caused by impaired compensating ability. Turner *et al.* observed that four patients who developed elevated ICP had increased variance over periods of thirty-three minutes prior to an ICP increase [7]. Several groups have found that an increase in the cardiac component[3] of the ICP signal precedes elevations [2,8]. Czosnyka *et al.* observed a short spontaneous decrease in ABP at the beginning of plateau waves in eleven of sixteen cases [9].

A few investigators have also attempted time series prediction of the ICP signal [10–12]. These attempts employed wavelet decompositions to separate the signal into different frequency bands followed by neural networks to predict the wavelet coefficients, which were finally used to construct the predicted signal segments. Although these methods were able to reproduce the cardiac component of the intracranial pressure, they were not able to accurately track trends, and the ability of these methods to predict rapid elevations was not reported.

Based on preliminary analysis of heart rate, ABP, and ICP spectrograms from four TBI patients, we noticed a significant change in the cardiac component of the ICP signal 10-25 seconds prior to an elevation in ICP. The following is a report of our detailed findings from eleven pediatric patients with severe TBI.

II. Methodology

A. Patient Population and Management

This study included eleven patients with head injuries who had a mean Glasgow Coma Scale (GCS) score of 6 (range 3–14) and were admitted to the pediatric intensive care unit at Doernbecher Children's Hospital. The study was reviewed and approved by the Institutional Review Board of Oregon Health and Science University, and the requirement for informed consent was waived. There were seven female and four male patients with an age range of 3 to 18 years (mean age 7.2 years). Nine of the patients survived. All patients received similar therapy based on generalized treatment guidelines for pediatric TBI [4].

B. Monitoring and Data Acquisition

Intracranial pressure (ICP) was monitored continuously using a ventricular catheter or parenchymal fiber-optic pressure transducer (Integra NeuroCare, Integra LifeSciences, Plainsboro, NJ). The ICP monitor was connected

[1]The CPP is defined as the difference between the systemic arterial blood pressure and the intracranial pressure, CPP = ABP − ICP.

[2]Ischemia is a decrease in blood supply caused by constriction or obstruction of the blood vessels or decreased blood volume.

[3]The cardiac component of the ICP signal is defined as the frequency components that are near the heart rate.

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Abstract

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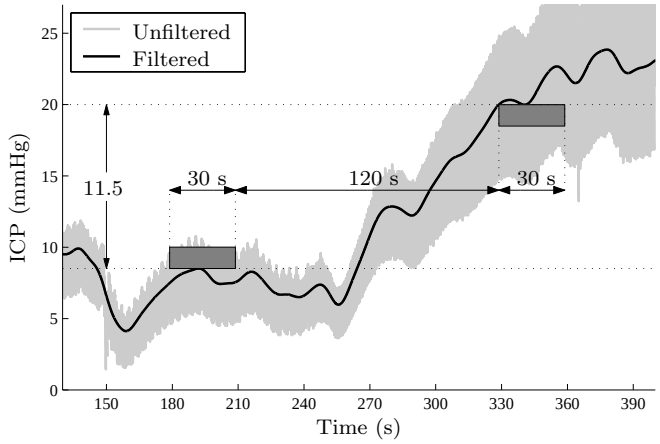

Fig. 1. Illustration of the criteria for a rapid and significant elevation in intracranial pressure. The ICP signal is shown before (gray) and after filtering (black). The range from the maximum value of the filtered signal in the first thirty seconds to the minimum value in the last thirty seconds had to be at least 10 mmHg. The filtered signal was also required to have a minimum value in the last thirty seconds of at least 20 mmHg.

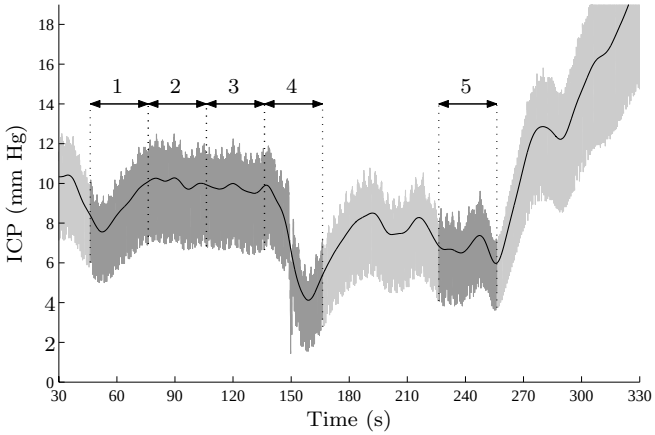

Fig. 2. Example of how the ICP signal was divided into five non-overlapping segments. We assumed that Segments 1–4 occur during a compensated physiologic state and Segment 5 occurs during the transition to an uncompensated state.

TABLE I

Summary of the six metrics used to characterize each of the five signal segments.

Segment Metric	Label	Source
Cardiac Peak Amplitude	C_{pa}	[2]
Cardiac Peak Frequency	C_{pf}	
Standard Deviation	σ_{ICP}	[7]
Average Pulse Amplitude	$\triangle_{\mathrm{ICP}}$	[2]
Average ABP	μ_{ABP}	[9]
Mean-Amplitude Correlation	ρ_{ma}	[6]

to an Agilent Merlin patient monitor (Agilent, Palo Alto, CA) which sampled the ICP and ABP signals at 125 Hz. An HPUX workstation automatically acquired these signals through a serial data network and they were stored in files containing six-hour epochs on CD-ROM [13].

C. Rapid Elevation Detection

We defined specific criteria for significant, rapid elevations in intracranial pressure. To capture the low frequency variations we first applied a lowpass filter with a cutoff frequency of 0.125 Hz. Any three-minute segment of this filtered signal that met the following two criteria qualified as a significant elevation in intracranial pressure: (1) the difference between the minimum value in the last thirty seconds and the maximum value in the first thirty seconds had to be at least 10 mmHg and (2) the minimum value in the last thirty seconds had to be at least 20 mmHg. The first criterion ensured that we only captured significant elevations of at least 10 mmHg that occurred over a period of no more than two minutes. The second criterion ensured that the elevation was large enough to be clinically significant [3]. These criteria are illustrated in Fig. 1.

D. Signal Characterization

Once the segments containing significant elevations were detected, we visually determined the leading edge of each elevation. The signal segment spanning the thirty-second segments prior to the edge of the elevation was compared to four other thirty-second segments spanning 90–210 seconds prior to the elevation. These segments were labeled in consecutive order 1–5, as shown in Fig. 2.

We assumed that any transition in physiologic state that occurs prior to an elevation begins no earlier than 90 seconds prior to leading edge of the elevation. Thus, the segments were chosen such that Segment 5 occurs during the hypothesized transition zone and Segments 1–4 occur during a compensated physiologic state.

We studied the ability of six different metrics to characterize the signal and distinguish between Segment 5 and the other four segments. These are summarized in Table I.

The cardiac component peak amplitude, C_{pa}, and frequency, C_{pf}, of the ICP signal was calculated by applying the fast Fourier transform (FFT) to each of the segments. Prior to applying the transform, the signal was downsampled by a factor of fifteen, the signal average was subtracted, the segment was multiplied by a Blackman window to improve precision of the estimate, and zero-padding was used to improve frequency resolution. Fig. 3 shows an example of the estimated power spectral density of each of the five segments shown in Fig. 2 over a frequency range near the heart rate. The frequency of the peak is approximately equal to the average heart rate of the segment.

The average pulse amplitude, $\triangle_{\mathrm{ICP}}$, was calculated as the average difference between the systolic and diastolic components of the ICP signal. The mean-amplitude correlation, ρ_{ma}, was calculated as the coefficient of correlation between the ICP trend and the average difference between the systolic and diastolic components of the ICP signal. The trend was calculated by lowpass filtering the ICP signal with a filter cutoff frequency of 1.25 Hz. The systolic and diastolic components were calculated by applying a weighted rank filter to find the 0.5 and 99.5 percentiles of the weighted signal and then applying a lowpass filter with

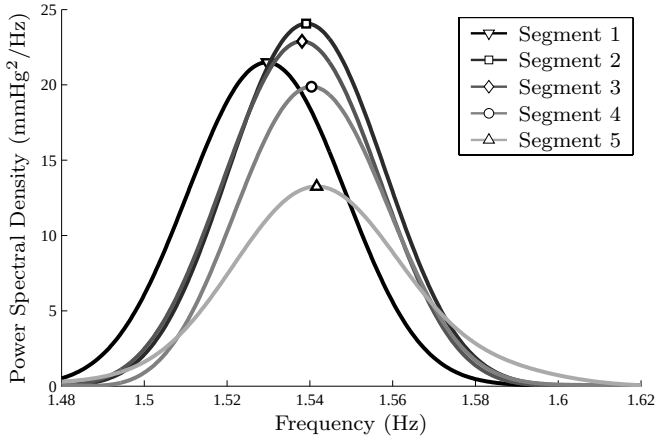

Fig. 3. Example of spectral estimation of the five segments shown in Fig. 2.

TABLE II

Number of significant elevations in which each metric for Segment 5 was less than, greater than, and more extreme than the four other segments. The p value is also listed. NS indicates that the result was not statistically significant. Thirty-three elevations found in eleven patients were included in this analysis.

Metric	S5 < S1–S4		S5 > S1–S4		Extreme	
	No.	p	No.	p	No.	p
C_{pa}	19	<0.001	7	NS	26	<0.001
C_{pf}	8	NS	15	<0.001	23	<0.001
σ_{ICP}	6	NS	10	NS	16	NS
$\triangle_{\mathrm{ICP}}$	12	0.008	9	NS	21	0.002
μ_{ABP}	5	NS	17	<0.001	22	<0.001
ρ_{ma}	13	0.003	2	NS	15	NS

cutoff frequency of 0.625 Hz. In all cases, the filters were applied forward and backward to eliminate phase distortion.

III. Results

Our detection algorithm found thirty-three rapid and significant ICP elevations in eleven different patients. A typical example of a detected elevation is shown in Fig. 1. For each elevation and each metric, we determined whether the metric for Segment 5 was less than, greater than, or in between the metrics for Segments 1–4. If the metric was less than or greater than the metrics of Segments 1–4, we counted it as an extreme value.

For our statistical analysis we assumed that metric values for each of the five segments were statistically independent and stationary. Our null hypothesis was that each of the segments were drawn from the same distribution. If the null hypothesis were true, then each of the five segments would have an equal probability of having the maximum, minimum, or extreme metric values. We used the binomial test with a 0.05 level of significance to determine if the null hypothesis could be rejected. The results are summarized in Table II.

Within the set of thirty-three elevations, we observed that the shape and characteristics of signals varied substantially from patient to patient, but was relatively consistent for each individual patient. This calls into question the binomial test assumption that the samples are independent. To determine if the results were still significant among the eleven different patients, we combined the metrics of all elevations detected for each patient and repeated the same test. We created the composite metrics by first scaling each set of metric values for the five segments to have zero mean and unit variance and then calculated the average for each patient. The results of this second test are summarized in Table III.

TABLE III

Number of significant elevations in which each composite metric for Segment 5 was less than, greater than, and more extreme than the four other segments. The p value is also listed. NS indicates that the result was not statistically significant. Eleven patients were included in this analysis.

Metric	S5 < S1–S4		S5 > S1–S4		Extreme	
	No.	p	No.	p	No.	p
C_{pa}	7	<0.001	2	NS	9	<0.001
C_{pf}	3	NS	5	0.012	8	0.006
σ_{ICP}	1	NS	3	NS	4	NS
$\triangle_{\mathrm{ICP}}$	4	NS	3	NS	7	0.029
μ_{ABP}	1	NS	8	<0.001	9	<0.001
ρ_{ma}	5	0.012	1	NS	6	NS

IV. Discussion

In this study we found that the cardiac component of the ICP amplitude, C_{pa}, and the mean-amplitude correlation, ρ_{ma}, were consistently lower in the thirty second segment at the leading edge of an ICP elevation as compared to segments 1.5–3.5 minutes prior to the edge. We also found that the heart rate, as measured by the cardiac component peak frequency, C_{pf}, and the average arterial blood pressure, μ_{ABP}, were consistently higher.

Our results seem to be inconsistent with the observations of previous studies discussed earlier. There are a number of possible explanations for these inconsistencies. One of the most important differences was that we found the variation in the ICP signal, as measured by the cardiac peak amplitude, C_{pa}, decreased just prior to an ICP elevation. All of the earlier studies that we are aware of found that various measures of the ICP amplitude increased prior to an ICP elevation [2, 7, 8].

Although the standard deviation, σ_{ICP}, is also a measure of the signal amplitude, it is not surprising that this was not a statistically significant precursor to ICP elevations because it is a coarse measure of variation and is unable to filter out effects due to respiration and changes in the heart rate that occur within the thirty-second segments. The average pulse amplitude, $\triangle_{\mathrm{ICP}}$, was significant when each of the thirty-three spikes were treated independently, but not when the metrics were combined for each of the patients.

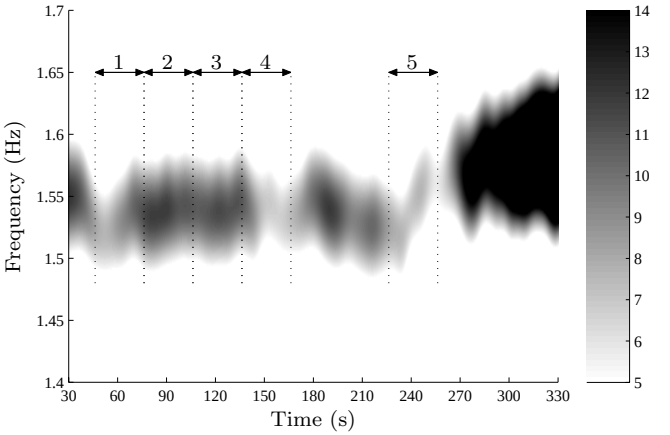

Fig. 4. Spectrogram of segment shown in Fig. 2. The spectrogram is an estimate of the power spectral density versus time of a nonstationary signal. The frequency range was chosen to show only the cardiac component of the ICP signal. Note that there is a clear decrease in the cardiac component at the leading edge of the ICP elevation and there is a clear increase afterwards.

The difference between the findings of earlier studies can partly be explained by a difference in the time scales. We examined signal segments ranging from 0–3.5 minutes before an increase in ICP elevation whereas some of the earlier studies measured the signal characteristics at intervals ranging from 15–30 minutes before an ICP elevation [2, 7].

Another key difference was the timing of the segments studied. We focused on segments immediately prior to a significant elevation. Due to the high sampling rate of the ICP signals, we were able to determine the onset of the elevation with high precision. In previous studies, it is likely that the observed increase in cardiac peak amplitude, C_{pa}, and mean-amplitude correlation, ρ_{ma}, were observed after the beginning of the elevation, but before the mean was actually elevated [2, 6, 8]. This is illustrated by the example in Figs. 1 and 2. Although we studied the signal prior to the onset of the spike at 256.2 s, the mean ICP does not actually rise to a clinically significant level until approximately 328 s. In the transition, the signal amplitude grows with along with the trend, which supports the findings of these earlier studies [2, 6–8]. This is also illustrated in the spectrogram of the same signal segment shown in Fig. 4.

Although Czosnyka *et al.* found that ABP dropped at the beginning of plateau waves, it is not surprising that it did not occur in this study since our criteria for rapid elevations does not distinguish between plateau waves and other types of ICP elevations [9]. It is well known that increased blood volume is the primary cause of ICP elevations, so it is not surprising that we found the ABP was usually elevated immediately prior to the ICP elevation [14].

V. Conclusion

The results of this study suggest that it may be possible to develop a predictor of rapid and significant ICP elevations. Although these results indicate that there are a number of statistically significant precursors to ICP, it is not clear how specific these metrics are to ICP elevations.

The physiologic significance of our results is unclear. The ICP signal changes are at least temporally related to the portion of the standard intracranial pressure-volume curve with significant slope and may well represent a transition zone where the physiologic mechanisms are shifting from a compensated to an uncompensated state just prior to an ICP elevation. Further studies are necessary to determine the underlying physiologic mechanisms represented by these ICP changes and the specificity and sensitivity of these methods for the prediction of rapid elevations.

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